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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques DUMAS et al.		Confirmation No.:	9096
Serial No.:	09/838,286	Examiner:	KWON, Brian Yong S.
Filed:	April 20, 2001	Group Art Unit:	1614

Title: HETEROARYL UREAS CONTAINING NITROGEN HETERO-ATOMS AS P38 KINASE INHIBITORS

REPLY BRIEF

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer mailed June 11, 2007, herewith is Appellant's Reply Brief.

The Reply Brief is presented in response to the following new points of argument raised in the Examiner's Answer:

1) On page 9, lines 13-15, of the Examiner's Answer, it is alleged,

> The nature of the invention is extremely complex in that it encompasses anticipating multiple complex disorders having unrelated manifestations and subsequently administering the instantly claimed plethora of compounds represented by the formula.

No evidence has been presented that any aspect of this invention is complex. Administering a compound of this invention to treat the p38 mediated diseases identified in the specification has not been shown to be complex and is clearly taught in the specification. Furthermore, no evidence has been presented that the identification of diseases mediated by p38 to be treated with the claimed compounds is complex. The large number of diseases already identified by those skilled in the art as mediated by p38 is inconsistent with this allegation.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Services as First Class Mail in an envelope addressed to: Commissioner of Patents, P O Box 1450, Alexandria, VA 22313-1450 on: July 31, 2007
Name: Richard S. Traverso
Signature: [signature]

2) On page 11, lines 2-5, of the Examiner's Answer, it is alleged,

> There are no known compounds of similar structure which have been demonstrated to treat (i) all types of diseases that are mediated through p38 or (ii) all types of disease other than cancer that are mediated thru p38. Since the assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits.

Proof that these assertions are not contrary to what is known in medicine can be found in the numerous prior art references which have been made of record. Most of the cited references describe urea compounds of a similar structure and similar broad utility. Most of these applications are assigned to pharmaceutical companies whose employees presumably are aware of what is known in medicine.

One example of a compound broad activity is the p38 inhibitor BIRB-796, which has been used in clinical trials to treat various inflammatory diseases.

3) The Examiner's Answer cites publications by Chialda et al.; Kapoun et al.; Feldmann; and Goodman et al, alleging that these publications provide evidence

a) p38 inhibitors are not useful in treating asthma, interstitial lung diseases and pulmonary fibrosis;

b) p38 inhibitors are hindered by drug toxicity in humans; and

c) the drug-drug interactions of p38 inhibitors are unpredictable.

Applicants addressed these allegations in the Brief on Appeal. The examiner has not responded to these arguments, so no further comments on these publications are necessary.

4) On page 13, lines 15-17, of the Examiner's Answer, it is alleged,

> As stated above, the specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for the treatment of all of the claimed disease conditions that are mediated by p38.

An *in vitro* p38 kinase assay is described on page 74 of the specification and an *in vivo* model is described on page 75. All exemplified compounds are said to have IC_{50} values ranging fro 1 nM to 10 μM on page 75. No evidence has been presented that this assay employed is not highly predictive for pharmaceutical use. It would not be in the assignee's interest to use anything but an effective assay.

5) The Examiner's Answer cites the case *In re Buting*, 163 USPQ 689 (CCPA 1969) in maintaining the rejection under 35 USC ' 112, first paragraph. The breadth of the instant claims and the evidence are different here from those present in *Buting*. In addition, substantial progress has been made in the study and treatment of cancer in the intervening years. These were found to be significant factors in reversing a rejection under 35 U.S.C. §§ 101 and 112 of claims that encompass the treatment of humans where the specification disclosed only *in vitro* studies and animal tests in *Ex parte Chwang*, 231 USPQ 751 (BOPA 1986).

6) On page 14, lines 1-3, and page 16, lines 3-5, of the Examiner's Answer it is alleged:

> Since the efficacy of the claimed compounds in treating all of the complex diseases [and] condition[s] may have unrelated manifestation[s] mentioned above [efficacy] cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study.

The painstaking experimental study the examiner refers to are clinical trials, which are routinely performed on a day-to-day basis on various compounds. Such routine tests clearly do not require undue experimentation.

7) On page 21, lines 1-5, of the Examiner's Answer, it is alleged,

> ...nexus between p38 inhibition and in vivo assessment of usefulness of p38 inhibition as anti-cytokine and anti-proteolytic enzyme in patients with the broadly defined "a disease mediated by p38" including asthma, pulmonary fibrosis and infectious disease (e.g. pneumonia and tuberculosis)...was not known at the time the invention was made.

Applicants note the citations made in the specification on page 2, last line, page 3, lines 1-2 and page 4, line 15. These citations demonstrate the nexus between asthma, pulmonary fibrosis and infectious disease was known at the time the application was filed, which is all that is necessary to satisfy 35 USC 112.

8) On page 21, lines 7-page 22, line 12 of the Examiner's answer it is alleged "applicants have not specifically described the compounds tested in the p38 assay" and they have not correlated the structure of the compounds tested with the relative activity.

Applicants have disclosed that all of the exemplified compounds are effective inhibitors of p38 on page 75 of the specification ("All compounds exemplified displayed p38 IC_{50}s of between 1 nM and 10 μM"). No further disclosure is necessary. More particularly, it is not necessary to report the relative values or correlate the structure of the compounds tested with the relative activity to enable one skilled in the art to make and use the invention since each compound is active. At these activity levels, other factors may be considered in selecting a compound. If however, an IC_{50} value for a particular compound is of interest, this value can routinely be determined by the assay described in the application.

9) It is alleged on page 21, line 17 of the Examiner's Answer that the 37 examples provided in the specification is not enough to support the scope of compounds claimed. However, no evidence has been presented to doubt that any compound encompassed by the claims is active. In the absence of such evidence, it is not necessary to provide even one example since the specification is presumed to be objectively enabling. The prior art references of record demonstrate that significant variations in portions of the structure of urea compounds can be made.

For the reasons stated above and in the Brief on Appeal, Appellants respectfully submit the subject matter of the claims on appeal satisfy the requirements of 35 U.S.C. §112, first paragraph. Therefore, Appellants respectfully request the outstanding rejection be reversed.

Respectfully submitted,

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